Birth of the first 100 babies in Hawaii after conception in-vitro: Experience at the Pacific In-Vitro Fertilization Institute

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This paper reports on the first 100 infants delivered consecutively the result of 63 pregnancies after conception in-vitro at the Pacific In-Vitro Fertilization (IVF) Institute. These pregnancies were established prior to the introduction of embryo-cryopreservation into the program. Ninety-seven percent (97%) of singleton pregnancies delivered after 36 weeks; only 5/31 (16%) required tocolytic therapy. The overall multiple gestation rate was 51%, higher than in many other IVF centers. Maternal complications and neonatal morbidity were associated primarily with these multiple gestations. Forty-one percent (41%) delivered in < 36 weeks, and tocolytics were administered in 22/27 (81%) of twin and 5/5 (100%) of triplet gestations. Neonatal morbidity was noted in 39 infants (33 from multiple gestations); 28 neonates were admitted to the intensive care unit (27 from multiple gestations). Nine births had or developed minor abnormalities (hernias, pyloric stenosis). One case of Trisomy 21, and one infant death at 11 months occurred in the group. The caesarean section rate for all IVF deliveries was 65%. It is concluded that IVF is clearly established in Hawaii for infertility refractory to other methods of treatment. The risk associated with IVF stem from the possibility of multiple gestations, not whether the pregnancy was initiated in-vitro. In the future, embryo cryopreservation may help to reduce the risk of multiple pregnancy.

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Introduction

Human In-Vitro Fertilization is now a well-accepted treatment for infertility due to tubal blockage, endometriosis, male factor, immunologic and idiopathic causes[1,2]. IVF has been offered in Hawaii since 1985 at the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children, and most health insurers in the State will provide coverage for at least one complete treatment cycle.

Since the first IVF birth in Hawaii in December 1985, more than 100 babies have been delivered (through July 1990). The overall clinical pregnancy rate at the Institute is high, compared to other programs in the United States[10], but an evaluation of the course of pregnancy and the delivery is also vital in evaluating the efficacy of this rapidly changing technology. This paper retrospectively summarizes data on the course of these first 100 IVF deliveries.

Patients and methods

Data on pregnancy, labor, and delivery and neonatal outcome were obtained from the treatment charts on the first 100 sequential IVF babies born. The average maternal age was 34 years (25-42 yrs). The mean duration of infertility was 6 years. Forty-seven (75%) patients had never delivered a viable fetus prior to IVF and 23 (37%) had never become pregnant.

Induction of ovulation was performed by controlled ovarian hyperstimulation with human menopausal gonadotropin (HMG), beginning either on cycle day 2 or following GnRH agonist (leuprolide acetate) suppression beginning on cycle day 21[4]. Oocytes were harvested either laparoscopically or, since November 1987, routinely while utilizing transvaginal

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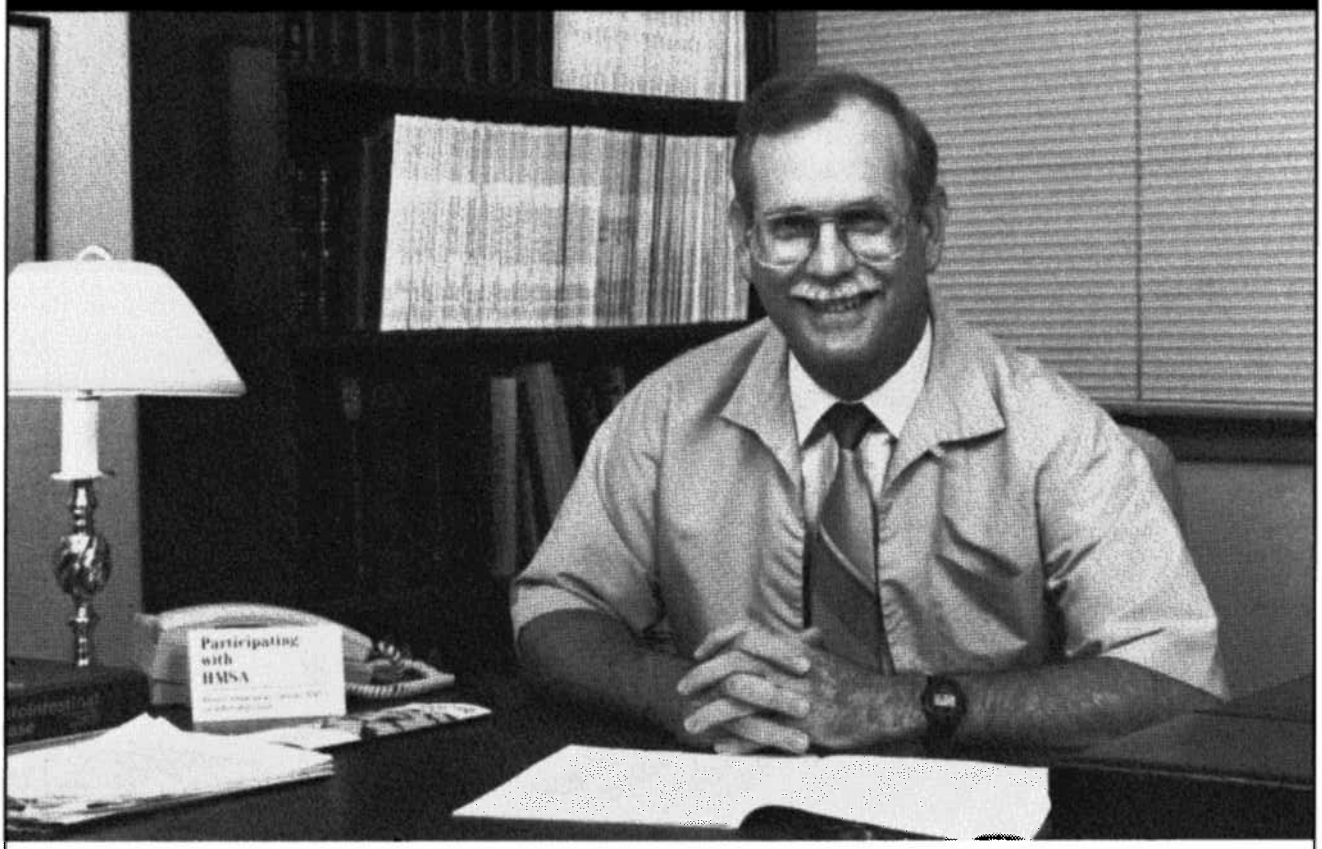

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ultrasonography, as an outpatient procedure. Oocytes were inseminated 4 to 20 hours after retrieval, and transfer of several of the embryos into the uterus was done typically at the 4-cell stage, approximately 48 hours after egg retrieval. Subsequent, early, quantitative HCG tests and real-time ultrasound at 6 weeks confirmed clinical pregnancy. Prenatal care was then carried out by the patient's private obstetrician.

TABLE 1
Infants Delivered

Singleton	31
Twin	27
Triplet	5
Male	54
Female	46

100 infants from 63 deliveries

TABLE 2
Causes of Infertility

Tubal Factor	31 (49%)
Anovulation	7 (11%)
Endometriosis	6 (10%)
Male Factor	4 (6%)
Unexplained	3 (5%)
Multiple Factors (*)	12 (19%)

* including antisperm antibody in several patients

Results

Between December 1985 and July 1990, 100 infants were born in 63 deliveries (Table 1). Multiple gestations accounted for 32/63 (51%) of total pregnancies (27 twins and 5 triplets). The sex ratio was unremarkable (54 males, 46 females). The primary cause of infertility in this cohort had been a tubal factor; other less frequent causes included anovulation, endometriosis, male factor, immunological, and unexplained infertility (Table 2) .

Most of the IVF pregnancies (78%) ended with delivery after 36 weeks (Table 3), including 97% of singletons and 59% of the multiple gestations. Of the 14 births occurring prematurely, eg <36 weeks, 13 were multiple. This comprised 41% of all multiple gestations. In the case of twins and triplets, the average gestational ages were 35 and 31. 5 weeks respectively. These exhibited a wide range of gestational ages, twins: 21 to 39 wks; triplets: 23 to 36 wks.

Maternal complications included preterm labor, gestational diabetes, active herpes infection, pregnancy-induced hypertension, and premature rupture of the membranes (Table 4) . The

TABLE 3
Duration of Gestation

Weeks	Total (n=63)	Singleton (n=31)	Multiple (*) (n=32)
< 28	2 (3%)	0 (0%)	2 (6%)
28-31	5 (8%)	0 (0%)	5 (16%)
32-35	7 (11%)	1 (3%)	6 (19%)
> = 36	49 (78%)	30 (97%)	19 (59%)

* mean gestational ages of 35 and 31.5 weeks for twins and triplets.

TABLE 4
Maternal Complications During Pregnancy

	Total (n=63)	Singleton (n=31)	Twins (n=27)	Triplets (n=5)
Tocolytics required in	32 (51%)	5 (16%)	22 (81%)	5 (100%)
Gestational Diabetes	7 (8%)	2 (6%)	4 (15%)	1 (20%)
Pregnancy-Induced Hypertension	5 (8%)	0 (0%)	4 (15%)	1 (20%)
Premature Rupture of Membranes	4 (6%)	0 (0%)	3 (11%)	1 (20%)
Active Herpes Infection	2 (3%)	2 (6%)	0 (0%)	0 (0%)
First Trimester Vaginal Bleeding	23 (37%)	ND	ND	ND
Postpartum morbidity*	11 (19%)	ND	ND	ND

* includes maternal fever and use of antibiotics; anemia requiring transfusion; transient renal insufficiency.

ND - not determined

latter two occurred only in the multiple pregnancy group. Only 5/31 (16%) of singletons required tocolytic therapy, compared to 22/27 (81%) in twins and 5/5 (100%) in triplets.

Multiple gestation with abnormal presentation was a major reason for the overall caesarean section rate of 65% (Table 5). The caesarean rate for twins and triplets was 89% and 80%, respectively.

Neonatal morbidity was documented in the case of 39 infants that were born (Table 6). Twenty-eight neonates were admitted to the neonatal intensive care unit at Kapiolani Medical Center, almost all the result of multiple births.

The reasons for extended hospitalization included severe prematurity, difficulty in feeding, respiratory problems, the need for antibiotics or hyperbilirubinemia. Two neonatal deaths occurred, one at 23 weeks in a triplet pregnancy and one at 24 weeks in a twin pregnancy. Additionally, 2 cases of intrauterine fetal demise took place, one at 21 weeks in a twin pregnancy, and one at 31 weeks in a triplet pregnancy associated with pregnancy-induced hypertension. Subsequently, one infant died at 11 months of age.

A summary of developmental abnormalities appears in Table 7. Minor abnormalities were observed in 9 (9%) of infants. This included 7 hernias and 2 cases of pyloric stenosis. Seven out of the total occured in multiple gestations. One case of Trisomy 21 developed in a triplet pregnancy.

TABLE 5
Indications for Caesarean Sections*

Multiple gestation with abnormal presentation	18
Cephalopelvic disproportion	5
Placenta previa	4
Single pregnancy with abnormal presentation	3
Abruptio placentae	2
Active herpes infection	2
Fetal distress	2
Chorioamnionitis	1
Severe pregnancy-induced hypertension	1
Elective	3

* number of cases. Total n = 41 (65% of cases)

TABLE 6
Neonatal Morbidity and Mortality

Neonatal morbidity*	39 (39%)
Singletons	6 (6%)
Multiples	33 (33%)
Admission to neonatal intensive care unit	28 (29%)
Singletons	1 (1%)
Multiples	27 (27%)
Neonatal mortality	2 (0%)
Infant mortality	1 (1%)

* causes include severe prematurity, difficulty in feeding, respiratory problems, use of antibiotics and severe hyperbilirubinemia.

** at 11 months of age.

TABLE 7
Infant Abnormalities

Minor:	
hernia	7
pyloric stenosis	2
Major:	
Trisomy 21	1

Discussion

Since the birth of the first IVF baby in 1978, human in-vitro fertilization has become an ethically and medically accepted treatment for infertility due to tubal disease, endometriosis, male factor, ovulatory dysfunction, immunological infertility and for unexplained causes[1,2]. Data presented here analyze retrospectively the outcomes in the first 100 IVF babies in Hawaii from the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children.

The multiple pregnancy rate of 51% reported here is higher than the range of 12 to 35% reported in other programs[5,9,11]. IVF clinical pregnancy rates upwards of 25%[2] only are achieved when several embryos are simultaneously transferred. Consequently, this increases the chances for multiple gestations[5,6,7] which, in turn, are associated with a higher incidence of maternal and fetal complications[8]. The high rate of multiple gestations in our series is probably due to transferring an average of more than 3 embryos at a time. This strategy evolved in response to the one-time-only insurance benefit allowed by most insurers in the State of Hawaii, combined with the lack of embryo-cryopreservation at this stage of the program's development.

At the Pacific IVF Institute, couples are counseled extensively regarding the risks and options, and they participate actively in the choice of the number of embryos at transfer.

Since January 1990, embryo cryopreservation has been offered at the Institute. This may significantly reduce the rate of multiple pregnancies. However, since worldwide experience has shown that a minimum of 3 embryos are required to optimize even singleton pregnancy rates in fresh transfer cycles[7], the risk of multiple pregnancy will probably continue until non-invasive methods of assessing embryo potential are developed. Until then, systematic identification of other factors pre-

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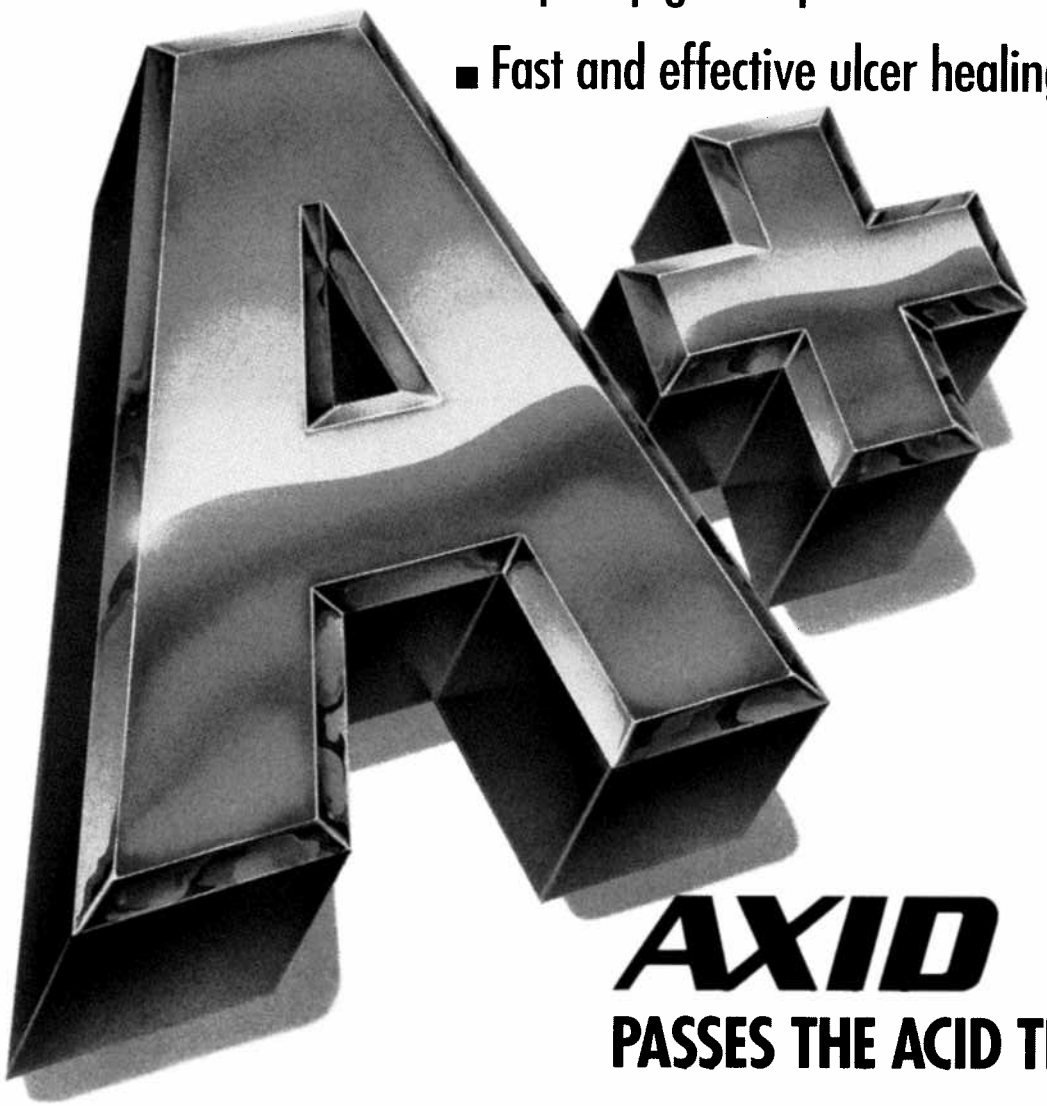

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IN-VITRO BIRTHS *(Continued from page 361)*

disposing to multiple IVF pregnancies, eg, maternal age, prior history of pregnancy, etc, may, in conjunction with cryopreservation, help to reduce the risk of multiple pregnancy.

Data indicate that multiple gestations account for the majority of maternal complications. The 22% pre-term delivery rate (<36 weeks) observed here is similar to that reported from other programs[9,10,12,13]. As expected, the rate was much higher for multiple gestations (41%) than for singletons (3%). However, older maternal age, in addition to multiple gestation, probably contributes to a high pre-term incidence of labor and delivery compared to primiparous patients who are not infertile. The incidence of first trimester bleeding, pregnancy-induced hypertension, premature rupture of membranes, and gestational diabetes is lower in our cohort than has been reported elsewhere[10]. Our data support the conclusions by Barlow et al[14] and Hill et al[13] that such complications are no more prevalent than in other populations of patients with infertility treated by other means. However, the comparatively high use of tocolytics reported in our series (51% of cases) is most certainly due to the relatively higher rate of multiple gestations than has been reported in other centers.

The higher multiple pregnancy rate also accounted for a high overall caesarean section rate (65%); 89% and 80% of twin and triplet pregnancies respectively, were delivered by caesarean section. Other authors have reported overall caesarean section rates of 33 to 56% in IVF gestations[9,11,12].

The overall incidence of neonatal morbidity (9%) is nearly identical to that reported by Yeh et al[10] who reported an 8.6% incidence, including pyloric stenosis, bilateral inguinal hernias and tibial torsion. Hernias and pyloric stenosis occurred in our series.

Summary

There have now been more than 100 live births from in-vitro fertilization performed at the Pacific In-Vitro Fertilization Institute at Kapiolani Medical Center for Women and Children in Honolulu. Although our overall clinical pregnancy rates are comparable or better than those at other well-established programs on the Mainland, multiple gestation remains one of the major challenges associated with higher rates of pregnancy. The rates and types of complications, however, are similar to those reported in other IVF centers and for other treatment modalities for infertility. Clearly, it is the presence of multiple gestations, and not whether the pregnancy was initiated in vitro, that should be viewed as the most important risk factor for complications in women with infertility who are treated by IVF[13]. Advances in embryo-cryopreservation and the identification of risk factors may help to reduce the incidence of multiples in the future.

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IN-VITRO BIRTHS *(Continued from page 363)*

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